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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,362	04/23/2001	Kazuma Tomizuka	081356/0158	4670

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EXAMINER

TON, THAIAN N

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 10/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/763,362

Applicant(s)

TOMIZUKA ET AL.

Examiner

Thaian N. Ton

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 July 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26-83, 85, 93, 96-112, 117-124, 126, 135, 136 and 138 is/are pending in the application.
- 4a) Of the above claim(s) 26-83 and 85 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 93, 96-112, 117-124, 126, 135, 136 and 138 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>7/5/05; 4/7/04</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 7/14/05 has been entered.

Claims 94, 95, 113-116, 125, 127-134, 137 and 139-143 are cancelled; claims 26-83, 85, 93, 96-112, 117-124, 126, 135, 136 and 138 are pending; claims 26-83 and 85 are withdrawn from further consideration as being directed to non-elected groups, Applicant timely traversed the restriction (election) requirement in Paper No. 8; claims 93, 96-112, 117-124, 126, 135, 136 and 138 are under current examination.

Information Disclosure Statement

Applicants' Information Disclosure Statement, filed 7/5/05 and 4/7/04, have been considered. Applicants have provided a partial translation of the reference of Mitsuya (Chapter IV: Germ line cell and Genomic Imprinting, Protein, Nucleic Acid, and Enzyme, 43(4): 573-582 (1998)). To the extent that the translation has been provided, this document has been considered.

Claim Rejections - 35 USC § 112

The prior rejection of claims 127-143 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is rendered moot in view of Applicants cancellation of the claims reciting the chromosome 21 fragment.

The prior rejection of claims 127-143 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is rendered moot in view of Applicants cancellation of the claims reciting the chromosome 21 fragment.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 93, 96-112, 117-124, 126, 135, 136 and 138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record advanced in the prior Office actions.

The instant invention consists of a recombinant chromosome, comprising the human chromosome #14 centromere of SC20, two telomere sequences, at least one recognition sequence for a site-directed recombination enzyme, at least two fragments from different human chromosomes, wherein each fragment comprises an antibody gene locus; and a marker gene, wherein the recognition sequence for the site-directed recombination enzyme is located between the chromosome fragments.

Applicants have submitted the biological deposit information with regard to the SC20 human chromosome #14 fragment and have amended the specification and claims with the information. The claims and specification fail to comply with the requirements of biological deposit, as set forth in 37 CFR §1.809 (d). IN particular, the claims and specification do not provide a description of what is particularly deposited, as a chromosome, in itself, would not be capable of reproduction. Furthermore, the amendment to the specification recites the

Accession Number, Date of Deposit, but there is no name and address of the depository (see part (4)). Applicants are requested to supply this information and amend the specification and claims accordingly.

Applicants argue that the claims now fulfill the enablement requirement. The Advisory Action, mailed 5/17/05, states that the first step in the generation of chromosome fragments is utilizing MMCT (microcell-mediated chromosome transfer), which results in the spontaneous fragmentation of chromosomes. For this reason, the Office stated that the methods, as claimed, are not found to be reproducible or predictable, and thus, require the deposit of the recited fragments, SC20, W23 and the 6-1 clone. Applicants argue that chromosome fragmentation is not always a necessary outcome of MMCT, and that is entirely possible, as shown in the working examples, to transfer a chromosome from one cell type to another, using MMCT without fragment it. Applicants conclude that because the working examples show that it is quite routine to screen for cells that have chromosome fragments, from those that contain intact chromosomes, MMCT does not always spontaneously fragment a desired chromosome. Applicants further point to Example 2 of the specification, showing that an intact human chromosome #22 was transferred into a mouse ES cell. See p. 32, paragraphs 1-3.

The claims are not directed to intact chromosomes, they require specific fragments from human chromosomes that comprise a particular antibody gene locus. These specific fragments are then used to produce a recombinant chromosome. It is unclear from the teachings of the specification, and the specific examples that Applicants point to, if the clones that are used to truncate and cleave chromosomes #2 and #22 are the same clones, used repeatedly, or that these cells are made, identified, and isolated in each instance.

Applicants argue that the 6-1 clone in question is derived from the A9/#22 and contains an intact chromosome #22. Applicants point to Example 23, pp. 148-149, for support. See p. 32 of the Response. This example states that the 6-1 clone

was derived from the A9/#22 cells, obtained from Example 1. In fact, Example 2 provides specific guidance to the production of these clones, particularly showing that the human chromosome #22 was fragmented by irradiating these microcells, and the confirming the presence of specific genes using PCR (see pp. 98-99). Thus, from this reading of the specification, there is no indication that the 6-1 clone contains an intact chromosome #22, and the clone appears to be generated by irradiation of the A9/#22 microcells. It is finally reiterated that the claims are not directed to the use of an intact chromosome, as Applicants argue. The claims require the generation of specific, particular fragments, which encode specific, particular genes.

Applicants argue that, with regard to claims 93-126, the fragments of chromosomes 2 and 22 are not spontaneously generated, and thus, it is unnecessary and improper to limit the claims to the SC20, W23 fragments and 6-1 clone, because the Examples of the application detail the precise – and repeatable – methods by which fragments from chromosomes 2 and 22 are generated. Applicants summarize the pertinent examples. Applicants state the following: the entire human chromosome 22 was introduced into chicken DT40 cells, whereupon the human telomere sequence was inserted into its LIF gene locus. This process results in the cleaving of the chromosome at a specific telomere cite. See p. 33, part (a), Summary, of the Response. Likewise, Applicants state, that the entire human chromosome 2 was introduced into chicken DT40 cells and a human telomere sequence was inserted at its CD8A gene locus, and a precisely-defined chromosome 2 fragment was then obtained. See Example 95. Thus, Applicants conclude that to obtain the fragments from chromosomes 2 and 22, the methods described by the specification are generated in a site-specific manner, and that none of these fragments are spontaneously generated. See p. 34 of the Response. Applicants argue that methods for preparing the human artificial chromosome λ HAC is described in the working examples, particularly by insertion of a telomere sequence

into the LIF gene locus on the human #22 chromosome to obtain a human #222 fragment by telomere truncation. Furthermore, a loxP sequence was also inserted into the HCF2 gene locus on the human chromosome #22 fragment. See p. 34 of the Response. Applicants' Response focuses on the introduction of various sequences into the #22 fragments, and that these fragments can also be prepared using intact human #22 chromosomes, using a mouse A9/#22 cell described in the specification. See p. 35 of the Response. Applicants argue that the methods for preparing the human artificial chromosome κHAC is described in the present specification, particularly that a telomere sequence is inserted into the CD8A gene locus on the intact human chromosome #2 to obtain a human chromosome #2 fragment by telomere truncation. Again, the Response focuses upon modifications that can be made when using a mouse A9 cell with an intact #2 chromosome. See pp. 35-36. Applicants point to a co-pending application (10/477,471) which explains tat the telomere insertion sites and the loxP sequences sequence described in the response are not limited to the sites in the present examples, and show telomere sequence insertion in other regions of human chromosome #22. See pp. 36-37. Thus, Applicants conclude that based upon these arguments and the description in the instant specification, and knowledge in the art, it is apparent that the human artificial chromosome of the present invention can be produced using an intact human chromosome #2 or #22, and that the insertion sites for telomere sequence and loxP sequence are not limited in the production of the human artificial chromosome of the present invention. See pp. 36-37.

These arguments are partially persuasive. The working examples, cited by Applicants, are unclear. For example, Example 82, which describes the transfer of human chromosome #22 into chicken DT40 cells, recites using mouse A9 cells containing the human chromosome #22 marked with a G418 resistance gene. See p. 270, 1st paragraph. Example 30, which teaches the generation of the 6-1 clone, names it the A9/#22 with G418 resistance, and that this clone is identified in

Example 26. See p. 157. Example 26 refers to the re-marking of the G418 resistance-marked human chromosome #22 cells with a puromycin resistance and particularly, that the A9 cells used are obtained in Example 1. Examples 1-2 are directed to producing mouse cell clones containing particular human chromosomes. Example 2 refers to the mouse A9 cell clone with the human chromosome #22, as "A9#22". Thus, it is unclear from Applicants' examples and arguments if the A9/#22 of Example 82 is directed to the same cell clone as those described in Examples 20, 26, and 2. The arguments are only found to be partially persuasive, because it is unclear if the Examples referred to in the Response, are the truncation or fragmentation of the chromosome fragment after the isolation of the initial, 6-1 clone. Likewise, with regard to Applicants' arguments for obtaining particular fragments from human chromosome 2, Applicants point to Example 95. Example 95 teaches the insertion of a human telomere sequence to the CD8A locus of a full-length human chromosome #2. This example discusses utilizing a chicken DT-40 cell retaining the full-length human chromosome #2. The instant specification refers to DT-40 chicken cells, retaining the full length chromosome #2, and refer to Kuroiwa *et al.* Kuroiwa *et al.* teach generation of the DT40 cells from mouse A9 cells using MMCT. What is unclear from the examples is whether the cells are generated *de novo*, or that they are the particular clone(s) that are isolated by Kuroiwa *et al.* Applicants are invited to provide an appropriate declaration, with specific guidance to either show that these clones are reproducible using the MMCT methods taught by the instant specification, or provide guidance to show that the examples are not all directed to uses of the same clone. The working examples appear to use a particular clone, which is an essential starting material, to produce the chromosome fragments that are instantly claimed. Thus, if these chromosome fragments are produced from clones that are not produced from repeatable method with which to generate these fragments. The specification only provides guidance for using MMCT to isolate particular cell clones, where the cell clones contain intact

chromosomes which can then be truncated or further modified to produce the instantly claimed fragments. However, this method does not represent a repeatable method with which to arrive at the claimed invention.

It is reiterated that these clones are essential to the claimed invention and that they are not obtainable by a repeatable method set forth in the specification or otherwise ~~be~~ readily available to the public.

If the deposit is to be made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the W23 fragment and the 6-1 clone have been deposited under the Budapest Treaty and that the W23 fragment and the 6-1 clone will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

- (a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
 - (b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
 - (c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request for the effective life of the patent, whichever is longer; and,
 - (d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807);
- and,
- (e) the deposit will be replaced if it should ever become inviable.

Once the deposit has been perfected, the claims will be limited to the SC20 and W23 fragments and the 6-1 clone.

Accordingly, in view of the lack of teachings or guidance provided by the specification with regard to the production of recombinant chromosomes have any two chromosome fragments, other than the exemplified chromosome 14, 2 and 22 fragments [SC20, W23 and fragment 6-1 clone], it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 93, 96-112, 117-124, 126, 135, 136 and 138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 93 is indefinite. The claim recites "the human chromosome #14 centromere of SC20, Accession Number ..." It is unclear what the Accession Number refers to, the human chromosome #14 centromere, or SC20. The claim is further unclear because it is unclear what the human chromosome #14 centromere of SC20 is. SC20 is a fragment of human chromosome #14, which contains its centromere. Appropriate correction is required. Claims 96-112, 135 depend from claim 93.

Claim 117 is indefinite. The claim recites, "a fragment of human chromosome #14 from SC20, Accession Number ..." in part (a) of the claim. This is unclear what the Accession number refers to. It is also unclear how the fragment of human chromosome #14 is from SC20. The specification teaches that SC20 is a

fragment of human chromosome #14, which contains its centromere. Appropriate correction is required. Claims 118-124, 126, 136 and 138 depend from claim 117.

Claim Rejections - 35 USC § 102

The prior rejection of claim 93 under 35 U.S.C. 102(b) as being anticipated by Tomizuka *et al.* [Nat. Gen., 16:133-143, 1997, cited in prior Office actions] is withdrawn in view of Applicants' arguments.

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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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